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Generic and therapeutic substitutions in the UK: are they a good thing?

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There is considerable interest and debate concerning the place of generic substitution (switching from a brand to generic product); and on therapeutic substitution, that is, switching to a cheaper, but apparently equivalent, product, usually within the drug class. Generic substitution by pharmacists is standard practice in UK hospital settings, and is being proposed for implementation in primary care. Although most prescriptions are already written generically (83% in the community in England in 2008), there are still cost savings that could be made if generic medicines are substituted against prescriptions written by branded name or by getting prescribers to adhere to advice to prescribe generically. Therapeutic substitution is more contentious, as direct evidence to support equivalence is normally lacking. However, the price differential between established drugs whose patents have expired and for which generics are available and newer, branded medicines within the same therapeutic class, makes therapeutic substitution an attractive application of cost-minimization analysis for the more efficient use of healthcare resources. Here we explore the tension that exists between the clinical appropriateness and safety of switching from an individual patient perspective and the consideration of value for money which is required to maximize population health from a health service perspective. Although substitution may affect individual patients (such as, for instance, reduced adherence, increased potential for medication error), it might be a price worth paying given the opportunity cost associated with the use of medicines that are clinically no better than cheaper alternatives.

Pressures in the system

In the UK there is much pressure from commissioners and providers of medicines in their various guises (general practices, Primary Care Organizations, Practice Based Commissioning groups, etc.) to make efficiency savings. This is felt much more keenly at a time when there is economic hardship and growth in allocations for health budgets are expected to be minimal. However, clinicians may be opposed to moves for generic or therapeutic substitution if they believe that therapeutic equivalence is unproven and patients may believe they are getting inferior drugs. Manufacturers of branded medicines are opposed and put up barriers to these initiatives as they see this as a potential threat to their profits.

In December 2007 a report from the House of Commons Public Accounts Committee criticized general practitioners (GPs) for continuing to prescribe branded, premium-cost products when they could be saving the NHS millions of pounds by switching to generic alternatives [1]. The report saw GPs as being too susceptible to drug company marketing and implied that secondary care physicians are not so susceptible and are also more restricted by hospital formularies. Many GPs would disagree with this as they see that the pressure to prescribe high-cost newer drugs often comes from consultants. They also see that postgraduate education sessions are largely sponsored by the drug industry, and local specialists, as key opinion leaders, inform GPs about new expensive products [2]. On occasion it appears that specialists themselves get upset when GPs switch patients to cheaper equivalent products [2, 3]. The National Audit Office (NAO) stated that £200 million could be saved if all Primary Care Trusts (PCTs) in England used a number of medicines in the same way, or at the same standard, as the 25% most efficient PCTs [4]. In particular this highlighted the use of generic simvastatin rather than other branded statins and aspirin as an alternative to clopidogrel (although a generic clopidogrel has subsequently emerged). The clear message was that all PCTs should be influencing and advising GPs to substitute

statins to save money. The use of low cost statins has become one of the Better Care, Better Value indicators of the Institute of Innovation and Improvement in England [5]. This advises that GPs can switch patients to low-cost statins provided there are no clinical reasons for them to remain on the more expensive drug, and increases pressure on NHS bodies to be seen to pursue actively productivity gains. The NAO published a follow-up report in May 2009 saying their recommendations had been successful, based on an estimate of the savings that PCTs had achieved through changing prescribing patterns in four therapeutic areas (statins, proton pump inhibitors, drugs that affect the renin-angiotensin system and clopidogrel) [6]. According to their calculations the total saving in 2008, across all PCTs in England, was £394 million [6]. The Association of the British Pharmaceutical Industry (ABPI) has been resistant to incentive schemes to stimulate switching by financial reward and mounted a legal challenge. In June 2007, the Department of Health, keen to promote money saving schemes, but wary about upsetting the drug industry and the potential legal implications, issued guidance on strategies to achieve cost-effective prescribing for PCTs in England [7]. This guide specifically looks at prescribing incentive schemes and advised the use of standard operating procedures, giving case examples of incentives for statin switches. It was said to be interim pending the outcome of the ABPI legal challenge. The European Court of Justice has since ruled that the prohibition could not apply to national public health authorities who have the responsibility of controlling public expenditure.

This challenge does not directly square with the ABPI's response to the consultation to proposals to implement direct generic substitution by pharmacists in the UK which has been negotiated as part of the Pharmaceutical Price Regulation Scheme (PPRS) from 2009. This proposes that 'subject to discussion with affected parties, the Department of Health will introduce generic substitution in primary care. This will enable pharmacists and other dispensers to fulfil a prescription for a branded medicine by dispensing an equivalent generic medicine. Provision will be made to allow the prescriber to opt out of substitution where, in his clinical judgment, it is appropriate for the patient to receive a specific branded medicine. In these circumstances, the named brand must be dispensed. Provision may also be made to exclude certain categories of medicines for clinical reasons in the interests of patient safety' [8]. The ABPI have supported this initiative but with exclusions from substitution in certain areas based on their view of patient welfare and international best practice [9]. Their suggested exclusions include modified or sustained release preparations, medicines with a narrow therapeutic window where there is evidence regarding the risk of adverse patient reactions or inadequate efficacy, vaccines, biosimilars and controlled drugs.

A further tension in the system is created by the recent policy in the NHS in England to promote the concept of patient choice [10]. The policy states that giving people more choice is a priority of the modern NHS. This follows research in the UK and overseas which has shown that treatments are more effective if patients choose, understand and control their care [11]. The choices highlighted include the right to be involved in decisions about healthcare and to be given the information needed to do this [11]. There are some arguments against this policy which have a bearing on moves to allow generic substitution and to encourage therapeutic switching. The first of these is that choice may reflect the desire of patients to access healthcare and treatments rather than strictly reflecting the needs of the individual or the effectiveness of interventions. Another concern is the costs or affordability of allowing choice in this way in a publically-funded healthcare system when resources are finite. For example, should patients be allowed to select an expensive brand name drug when a generic drug will do much the same? In Wales, the policy has been different, so that NHS bodies are encouraged to allow patient voice [12].

What is the evidence: generic substitution?

Generic prescribing is almost universally acknowledged as desirable and representing high quality prescribing in the UK. It has benefits that include reducing the risk of error as each drug has only one international chemical name rather than many brand names and, usually, reducing the cost of prescribing. There is little evidence that it detracts from patient care. European laws have meant that there has been a move from using British Approved Names (BAN) to Recommended International Non-proprietary Names (rINN), which has strengthened the safety argument and ensured that drugs of the same class have similar names which helps reduce confusion [13]. In the UK, hospital practice has been to use the generic name for most drugs, and this is increasingly the case in general practice. In 2008 in England, for example, over 83% of prescription items were prescribed generically (up from 35% in the mid 1980s), though only 65% were dispensed as generic products, either because only a brand product was available as the drugs are not 'off patent' or because no generic alternative was available [8].

Generic manufacturers normally submit applications to the regulatory authorities based upon the safety and efficacy data of the equivalent branded product. They have to demonstrate that the pharmacokinetics of the same molar dose of their product is within acceptable, predefined limits. This proof of bioequivalence is an important issue affecting both generic formulations and different brands of a particular drug. European regulations state that generic products must be shown to have bioavailability within the range of 80–125% of the reference product. Tighter limits can be set when safety is an issue. Generic

products must meet this standard to be considered 'essentially similar' to the originator brand [14]. Alternatively, a new brand of an established drug may be introduced without reference to the established brand, supported by its own data on bioavailability, efficacy and safety, and may, or may not, be bioequivalent to the original brand. A good example of this is the Qvar® CFC-free beclometasone inhaler, which is not bioequivalent with Becotide® [15].

Although most generic manufacturers endeavour to adhere to an agreed code of conduct that recommends similarity to the proprietary product, there is no binding requirement for different formulations of a drug to have a similar appearance. For this reason, generic drugs often differ from the originator brand and, likewise, brands from one another, as is the case for packaging. Unless warned that the appearance of their medicine has changed, this may cause patients alarm and raise fears that a prescribing or dispensing error has been made. In one comparison of generic and branded salbutamol inhalers, 45% of patients claimed to have been able to detect some difference between their usual Ventolin® inhaler and the blinded Ventolin® used in the study [16]. A survey in Germany found that 37% of patients expressed scepticism about generics because of their lower price and these patients were more likely to consider generic drugs inferior to branded products [17]. On the other hand, many people in the UK have now grown accustomed to their medication in generic form, evidenced by the high proportion of prescription items being dispensed generically.

The evidence extending bioequivalence of generic and branded medicines to therapeutic equivalence is rather poor, but overall supportive. For example, a systematic review and meta-analysis of clinical equivalence of generic and brand-name drugs used in cardiovascular disease identified 47 articles providing evidence on this topic, of which 38 were randomized, controlled trials [18]. Overall there was no evidence of superiority of brand name compared with generic drugs, aggregate effect size (n = 837) was −0.03 (95% confidence interval (CI) −0.15, 0.08). There are, however, several clinical areas or drug types where brand prescribing may be considered preferable because of the possibility of therapeutic inequivalence or potential for confusion (see Table 1). These cautions are usually highlighted by the British National Formulary (BNF) [15] or as part of national guidelines.

Table 1

Medicines for which prescribing by brand might be safer, more effective or reduce the risk of medication error

Reason not to substitute	Examples [15, 40]
Where there is a difference in bioavailability between brands of the same medicine, particularly if the medicine has a low therapeutic index	Ciclosporin, lithium, CFC-free beclometasone metered dose inhalers (Qvar® and Clenil Modulite®), carbamazepine
Where modified release preparations are not interchangeable	Prolonged release preparations of carbamazepine, theophylline, diltiazem, aminophylline, mesalazine, nifedipine, morphine and oxycodone
Where pharmacokinetic differences may be evident	Phenytoin
Where there are important differences in formulation between brands of the same medicine	Adrenaline pre-filled syringes, transdermal formulations of fentanyl, buprenorphine
Where products contain multiple ingredients and brand name prescribing aids identification	Combination topical preparations, hormone replacement therapy, oral contraceptives, pancreatin supplements, antacids preparations containing simeticone
Where there is a significant danger of medication error	Tacrolimus
Where administration devices (e.g. inhaler or self-injection) have different instructions for use and patient familiarity with the same product is important	Dry powder inhaler devices, insulin, apomorphine, estradiol transdermal patches, somatropin injection cartridges, alprostadil injection, interferons
Where different preparations of the same medicine have different licensed indications	Cyproterone (Androcur® or Cyprostat®), silfenafil (Viagra® or Revatio®), duloxetine (Cymbalta® or Yentreve®), bisoprolol (Cardicor® or Emcor®), buprenorphine (Temgesic® or Subutex®)
Where the product is a biological rather than chemical entity	Biosimilars, vaccine products

Epilepsy – a special case?

The area where there seems most debate is in the equivalence of generic and branded antiepileptic drugs (AEDs). The British National Formulary (BNF) states that bioequivalence should not be assumed for different brands of carbamazepine and phenytoin, stating: 'On the basis of single dose tests, there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients'. It also warns that, 'Different preparations of carbamazepine may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation.' [15]

A recent systematic review of studies comparing seizure events or seizure-related outcomes between one brand-name AED and at least one alternative version identified seven RCTs which were included in a meta-analysis [19]. The aggregate odds ratio (n = 204) was 1.1 (95% CI 0.9, 1.2), indicating no difference in the odds of uncontrolled seizure for patients on generic medications compared with patients on brand-name medications. In contrast, the observational studies included in the review, identified trends in drug or health services utilization that the authors attributed to changes in seizure control. There are

a few studies of patient preferences for generic *vs.* branded AEDs, the largest of which invited 356 patients to complete to a structured questionnaire [20]. It reported that 28% of respondents believe breakthrough seizures to be attributable to the use of generic AEDs, and 34% believing they increased adverse effects. However, a low response rate (50%), and possible framing effects (all questions related to generic medicines) does limit the interpretation of the results.

There seems a contradiction in guidance in this area in the UK; the NICE clinical guideline on epilepsy [21] endorses the BNF advice whereas the SIGN guideline on epilepsy states unequivocally that: 'formulations of AEDs are not interchangeable and generic substitution should not be employed' [22]. The Department of Health (DH) issued a statement in relation to the prescribing of lamotrigine that there is no compelling evidence to suggest that switching from the originator brand to a generic alternative will have an adverse clinical outcome [23]. The DH further recommended that prescribers modify their usual generic prescribing practice if, in their judgment, the circumstances of individual patients warrant such action. The charity Epilepsy Action encourages patients to ask their doctor to prescribe by brand to ensure consistency of supply [24].

Biosimilars and therapeutic equivalence

Biosimilar medicines are alternatives to biological medicinal products (typically recombinant therapeutic proteins) whose patents have expired. Six such products have been granted market authorization in the European Union, including those for somatropin growth hormone, erythropoietin and granulocyte colony stimulating factor. At first sight it may seem reasonable that products of this nature can be developed as exact copies by different drug companies, but this may not be the case in practice. They are large, complex molecules, manufactured using processes such as cell cultures and recombinant DNA technologies, and consequently the composition of products may vary significantly, resulting in potential differences in immunogenicity that may affect efficacy and safety. This has been seen before with epoetins, where pure red cell aplasia developed after a small change in the manufacturing process [25].

Consequently, the European Medicines Agency (EMA) has stipulated that approval or licensing of each of these products has to be based on evaluation of full sets of independent data [26], including a post-marketing pharmacovigilance plan to monitor safety and any immunological responses [27]. This requirement is stricter than the evidence on bioequivalence required for the licensing of small molecule generic drugs. However, the EMA does accept non-clinical evidence, such as from studies of healthy volunteers in the case of recombinant granulocyte colony stimulating factor, and allows for extrapolation to other indications of the reference medicinal product without specific evaluations in the relevant populations [28].

EMA's guidance on safety requirements for prescribing of the biosimilar products [29] specifies that the decision to treat a patient with a reference or a biosimilar medicine should be taken 'following the opinion of a qualified healthcare professional' [29], in order to discourage routine substitution. Most European countries have either established legislative measures to prohibit generic substitutions of biologics or given regulatory advice on their use (including prescription by brand).

What is the evidence: therapeutic substitution?

The agenda has been driven mainly by statins, which cost the NHS in England (community dispensed prescriptions) over £450 million in 2009, about £75 million of which was on branded products. The recommendations of the NAO on the therapeutic substitution of statins, and the concept of 'better care, better value' indicators has been met with some concern in certain quarters. An observational study conducted by Pfizer, and authored by Pfizer employees, was published in an attempt to provide evidence for potential problems with switching statins [30]. Based on an analysis of The Health Improvement Network (THIN) database, the outcomes of patients who had been on atorvastatin for more than 6 months were compared between those who were switched to simvastatin, and matched controls who remained on atorvastatin. The risk of death or first major cardiovascular death was estimated to be 30% higher in the switched group (hazard ratio 1.3, 95% CI 1.02, 1.64), as was discontinuation of therapy (21% per year *vs.* 8% per year; $P < 0.001$). However, the study had major limitations in that the reasons for switching were not available for analysis, nor were the reasons for discontinuation of therapy. In these patients it might be expected that outcome is worse. It is also highly likely that patients were switched for a good reason rather than in a planned approach to save money. There is also a clear suggestion that the groups were unequal at the time of switching – 60% of the switched patients were achieving QOF target at time of the switch *vs.* 74% of those who remained on atorvastatin [30].

Studies of statin switches are hampered by lack of randomized controlled trials and tend to be supported by industry funding. Two independent studies, with very different conclusions, include an observational study from an English PCT and a practice-based audit.

The first assessed the correlation between the use of generic statins for secondary prevention and two QOF targets [31]. A significant correlation between statin choice and target achievement was observed $\rho = -0.26$, $P = 0.028$,

Table 2

Dose equivalent reductions in LDL cholesterol as a basis for the therapeutic substitution of statins. Adapted from Law *et al.* [37]

Reduction in LDL cholesterol*	21–24%	27–29%	31–33%	37–38%	42–45%	48–49%	53–55%
Mean absolute reduction (mmol l^{-1})†	1.02–1.31	1.30–1.40	1.51–1.60	1.77–1.84	2.01–2.15	2.32–2.36	2.56–2.64
			Dose mg (Cost £ for 28 days) [15]				
Simvastatin	–	10 (£0.95)	20 (£1.02)	40 (£1.40)	80 (£3.27)	–	–
Pravastatin	20 (£2.22)	40 (£3.02)	–	–	–	–	–
Atorvastatin	–	–	–	10 (£13.00)	20 (£24.64)	40 (£24.64)	80 (£28.21)
Rosuvastatin	–	–	–	5 (£18.03)	10 (£18.03)	20 (£26.02)	40 (£29.69)
Fluvastatin	20 (£8.41)	40 (£9.97)	80 (£19.94)	–	–	–	–

*Percentage reductions are independent of pre-treatment LDL cholesterol concentration. †Absolute reductions are standardized to usual serum LDL cholesterol concentration of 4.8 mmol l^{-1} before treatment (mean concentration in trials).

suggesting poorer achievement by generic products. Importantly, however, the analysis did not control for any potential confounding factor, and did not assess the switching of statins when used for primary prevention. For example, a confounding factor may be that a higher proportion of branded statins are prescribed by dispensing practices to healthier rural patients.

The second assessed patients who were switched from atorvastatin to simvastatin, to determine whether switching was appropriate [32]. At 2 years follow-up, 61 (94%) of the 65 patients still registered at the practice, were still on simvastatin and 58 (89%) were on the same dose. There was no significant change in mean total cholesterol (4.04 $\pm$ 0.52 mmol l^{-1} prior to the switch and 3.90 $\pm$ 0.63 mmol l^{-1} at follow-up; $P = 0.06$), though the retrospective nature of the analysis and small sample size are clear limitations. A questionnaire survey of participant's views (though with a limited response rate) suggested that they were quite happy to change treatment and saw benefit in terms of cost-savings for the NHS [32]. This supports anecdotal evidence that people are willing to switch medication if the reasons are carefully explained.

From a population health perspective, the significant price differential between branded and generic statins, coupled with their high volume of use, requires cost-effectiveness to be an important consideration. Even if older products are marginally less effective, their greater cost-effectiveness can benefit the wider population [33]. However, for standard-dose therapy (simvastatin 40 mg, atorvastatin 10 mg) this argument is largely irrelevant as the evidence demonstrates that they are equally effective at lipid-lowering and equally well tolerated [34]. The UK-based Heart Protection Study, the largest study on statins involving over 20 000 participants, clearly demonstrated that simvastatin given at a dose of 40 mg daily was safe and highly effective for people with a range of risks, and very well tolerated [35]. This has been the approach adopted by the NICE Guideline on Lipid Modification for England and Wales which recommends a dose of simvastatin 40 mg for most people without the need to pursue targets for cholesterol reduction [36]. The body of clinical evidence, synthesized in a systematic review and meta-analysis [37], supports the comparability among various statins, and is summarised in Table 2.

Clearly, most cases of therapeutic switching are dependent on the availability and timing of introduction of cheaper generic products. Simvastatin, whose UK patent expired in 2003, and price decreased with the availability of generics, has been the preferred statin to switch to. With atorvastatin's UK patent expected to expire in November 2011, however, it is unclear how future switching of statins will evolve.

Category M *vs.* 'branded generics': chasing prices

The principle for substituting branded products for therapeutically equivalent alternatives is that of cost minimization analysis, which is dependent on the notion of equal outcomes at reduced cost. However the prices of generics in the UK are not static. Up until April 2005, generic manufacturers set their own price for a generic product, usually a competitive price, relative to prices set by other companies. The Drug Tariff, which is a tariff outlining what will be paid to contractors (pharmacists or dispensing GPs) for medicines or products supplied on an NHS prescription, then sets a price for reimbursing the likely costs spent on these products. This was previously solely based on a basket of average prices from a range of manufacturers (prices are listed as Category A products). In April 2005 new arrangements for calculating the Drug Tariff for many commonly used generics came into force in England and Wales. The changes were introduced as a part of the process of implementing the new pharmacy contract for 2005/06 which sought to separate more clearly how pharmacists were paid from the profit they could generate from purchasing drugs at a discount and then subsequently getting full reimbursement. On a quarterly basis some drugs go into the Category M basket while others are removed, and also some drugs within the basket have their price adjusted. This may have the beneficial effect for the NHS of more rapidly reducing drug prices

shortly after patent expiry, if a generic product is available. However a knock on effect is that it difficult for planning and budgetary control in Primary Care Organizations (PCOs) and in general practice; for example formulary choices based on cost-effectiveness may vary substantially from one quarter to the next. A further complexity is that the pricing for 'branded generics' may undercut the Category M price for an equivalent generic drug [38]. Branded generics are off-patent drug sold under a brand name (not the original). Those priced below Drug Tariff price for the generic equivalent are an attractive option for PCOs and practices trying to keep drug prices down but such savings may be transient as the manufacturer can increase the price at relatively short notice [38]. It is also important to reflect that prescribing by brand in such cases, even if as a branded generic, where there is a generic product available, runs counter to years of effort in the NHS to promote generic prescribing. It can be argued that the pricing system for drugs set by the Department of Health now creates anomalies which contradict best practice in the NHS.

Conclusions

The UK now has one of the highest rates of generic prescribing in the world (83% in the community in England in 2008). The main drivers for this in the NHS may be the historic belief in generic prescribing in medical schools and hospitals and that generic drugs are generally cheaper than their branded counter-parts. Generic substitution is standard practice in secondary care, and recent proposals to introduce generic substitution by pharmacists dispensing prescriptions in primary care, if accepted, should result in cost savings [39]. These are to be welcomed. However, there are cases where generic prescribing may not be appropriate, and in these cases drugs should be prescribed by brand name to ensure continuity of supply of a particular product and to avoid potential lack of effect, adverse effects due to toxicity or poor patient understanding, co-operation and adherence.

Therapeutic substitution is more contentious, but there are also considerable cost savings to be made by switching to a cheaper, apparently equivalent product, usually within the drug class. Evidence relating to statins, where the greatest drive towards therapeutic substitution has been, and where the greatest cost savings may be achieved, does not suggest that harm arises from such switches, but the drug substituted may be less convenient and can conflict with patient-centred care and patient choice. Thus, the trade-off is patient choice *vs.* the release of funds that could be better used elsewhere (generic simvastatin 40 mg is currently thirteen times less expensive than rosuvastatin 5 mg). Arguably, within any universal, publicly-funded healthcare system, where population health benefits are to be maximized subject to a budget constraint, the latter should be the priority.

Competing interests

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